Detect Protect andCorrect
Venice Arrhythmias 17 Oct 2015

Protecting against AF related stroke

Dhiraj Gupta MD DM FACC FRCP
Consultant Cardiologist
Liverpool Heart and Chest Hospital

Imperial College London

ICMS The Institute of Cardiovascular Medicine and Science

October 16 - 18
14th EDITION 2015

MY CONFLICTS OF INTEREST ARE

Research Grants, Hospitality and
Speaker Fees from Biosense Webster Inc.
Proctor fees from St Jude Medical Ltd

AF and Stroke

- AF patients are twice as likely to die
  - 30 day mortality 25% vs 14%

- AF patients are three times as likely to be severely dependent after a stroke
  - At 12 months 30% vs 10.9%

Lin *et al* (1996) *Stroke*;**27**;1760-4

Warfarin reduces the risk of stroke in both primary and secondary prevention

Meta-analysis of trials comparing dose-adjusted warfarin with placebo

	Primary prevention	Secondary prevention	All trials
Number of trials	5	1	6
Patients (n)	2461	439	2900
ARR with warfarin vs. placebo (%)	2.7	8.4	3.1
RRR with warfarin vs. placebo (%)	62	68	64
NNT	37	12	32

ARR = absolute risk reduction; NNT = number need to treat for 1 year to prevent one stroke; RRR = relative risk reduction

Hart RG et al. Ann Intern Med 1999;131:492–501; Ann Intern Med 2007;146:857–67

Sentinel Stroke National Audit Programme (SSNAP) data for UK Apr 2014-Mar 2015

Total patients with stroke	**79721**
Known Atrial Fibrillation (AF) before stroke	**16339(20.5%)**
If AF before stroke,	
On anticoagulant medication	**6763 (41.4%)**
Not on OAC	**7231 (44.3%)**
No but	**2345 (14.4%)**
If AF before stroke,	
Only on anticoagulant medication	**6047 (37%)**
On OAC and antiplatelet drugs	**716 (4.4%)**
Only on antiplatelet drugs	**5515 (33.8%)**
On neither	**4061 (24.9%)**

Quality Outcomes Framework (QOF) Data

8020 GP practices in England, population 56,012,096

- AF 001, AF prevalence: 849,407 (1.5%)
- AF 002, CHADS risk assessment, 97.5%
- AF 003, OAC or ASA in CHADS score ≥1, 93%
- AF 004, OAC in CHADS score ≥1, 69.1%

- Exception reporting
  - AF004, 17%

2013-2104 data, Source hscic.org.uk, published 28 Oct 2014

Problems with warfarin

- Unpredictable Effect
  - Interaction with food, alcohol and drugs
  - Time in therapeutic range only 50-60%
- Bleeding
  - doubles the risk of intracranial bleeding
- Slow Onset of Action
- <50% of eligible patients are on Warfarin

Novel Oral Anticoagulants

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation

Issued: March 2012

NICE technology appr
guidance.nice.org.uk/ta249

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

Issued: May 2012

NICE technology app
guidance.nice.org.uk/ta256

Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation

Issued: February 2013

NICE technology apprais
guidance.nice.org.uk/ta275

Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation

Issued: September 2015

NICE technology appraisal guidance 355
guidance.nice.org.uk/ta355

Clinical pharmacology

	Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Food effect on bioavailability	No	Yes (Taken with food)	No	No
Renal clearance	85%	~33 %	~27%	~50%
Dialysis	Dialysable	Not dialysable	Not recommended	Not recommended
Mean half-life ($t_{1/2}$)	12–14 h	11-13 h in elderly 5-9 h in young	~12 h	10-14h
T_{max}	0.5–2 h	2–4 h	3–4 h	1-2h

Much to commend NOACs

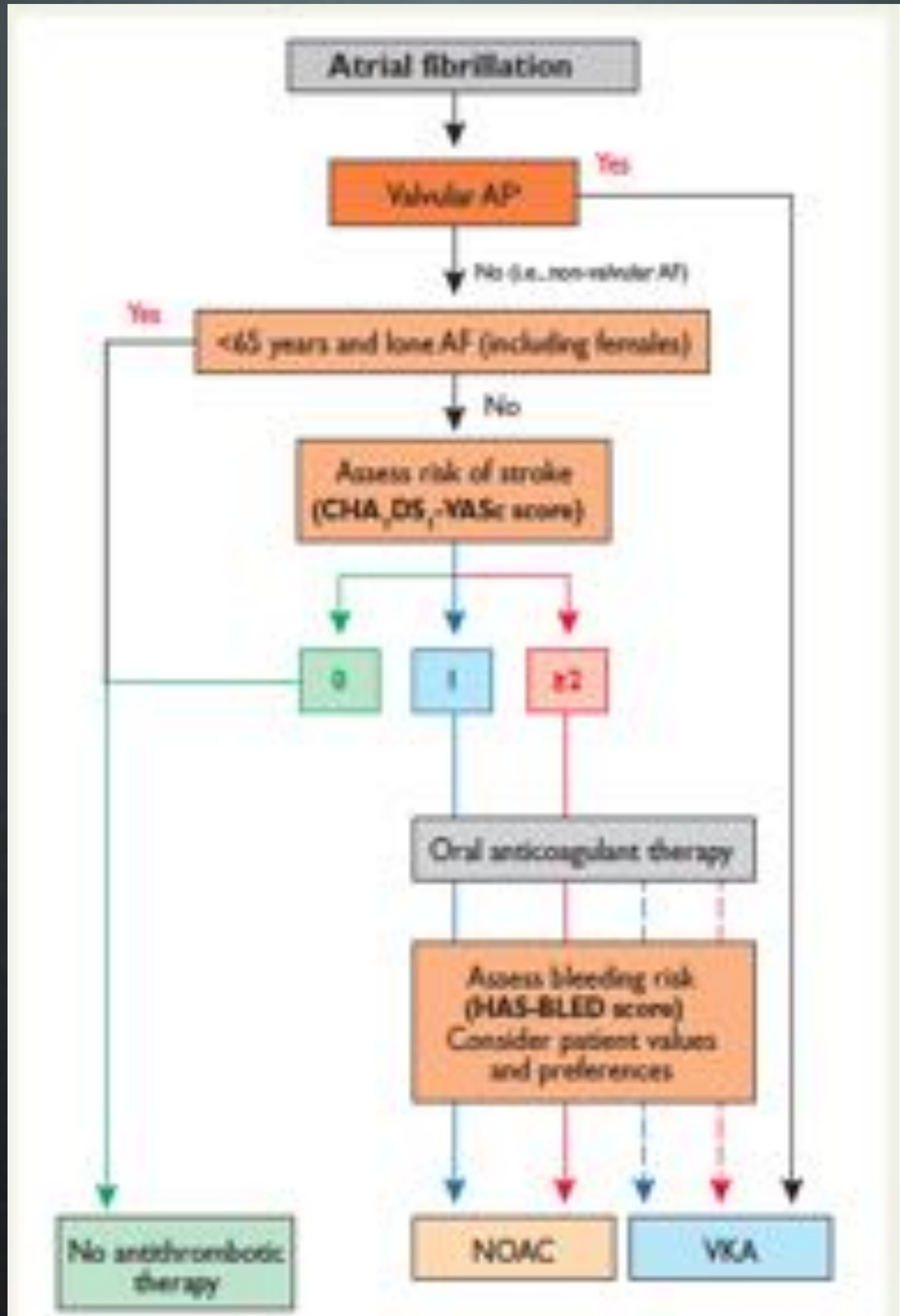
- Rapid onset of action (few hours)
- No coagulation monitoring needed
- Minimal drug interactions
- Superior or comparable efficacy to Warfarin in Stroke Prevention
- Lower risk of intracranial bleed compared to warfarin

Trial data with NOACs vs warfarin

	Dabigatran	Rivaroxaban	Apixaban
Trial	RE-LY n=18,100 2 years	ROCKET-AF n=14,200 1.5 years	ARISTOTLE n=18,200 1.8 years
Dose	150mg BD or 110mg BD	20 mg OD	5 mg BD
Stroke or systemic embolism	D150 1.11% vs 1.69% (superior) D110 1.53% vs 1.69% (non-inferior)	2.12% vs 2.42% (non-inferior)	1.27% vs 1.60% (superior)
Hemorrhagic Stroke	D150 0.10% vs 0.38% (P<0.001) D110 0.12% vs 0.38% (P<0.001)	0.26% vs 0.44% (P=0.024)	0.24% vs 0.47% (P<0.001)
Ischaemic or uncertain stroke	D150 0.92% vs 1.20% (P<0.03) D110 1.34% vs 1.20% (P=0.35)	1.34% vs 1.42% (P=0.581)	0.97% vs 1.05% (P=0.42)
All-cause mortality	D150 3.64% vs 4.13% P=0.051 D110 3.75% vs 4.13% P=0.13	4.52% vs 4.94% P=0.15	3.52% vs 3.94% P=0.049

Results presented as 'NOAC(%) vs warfarin(%)'

There are no head-to-head studies between these agents. There are limitations such as differing patient populations, designs and outcomes, and caution should therefore be exercised when interpreting these findings. No conclusions about the relative efficacy or safety of any of these agents should be drawn from these data
Please refer to individual product SmPCs for further information


Atrial fibrillation
Valvular AF
Yes
No (i.e. non-valvular AF)
Yes
<65 years and lone AF (including females)
No
Assess risk of stroke
(CHA2DS2-VASc score)
0
1
≥2
Oral anticoagulant therapy
Assess bleeding risk
(HAS-BLED score)
Consider patient values
and preferences
No antithrombotic
therapy
NOAC
VKA

Atrial fibrillation: the management of atrial fibrillation

Issued: June 2014

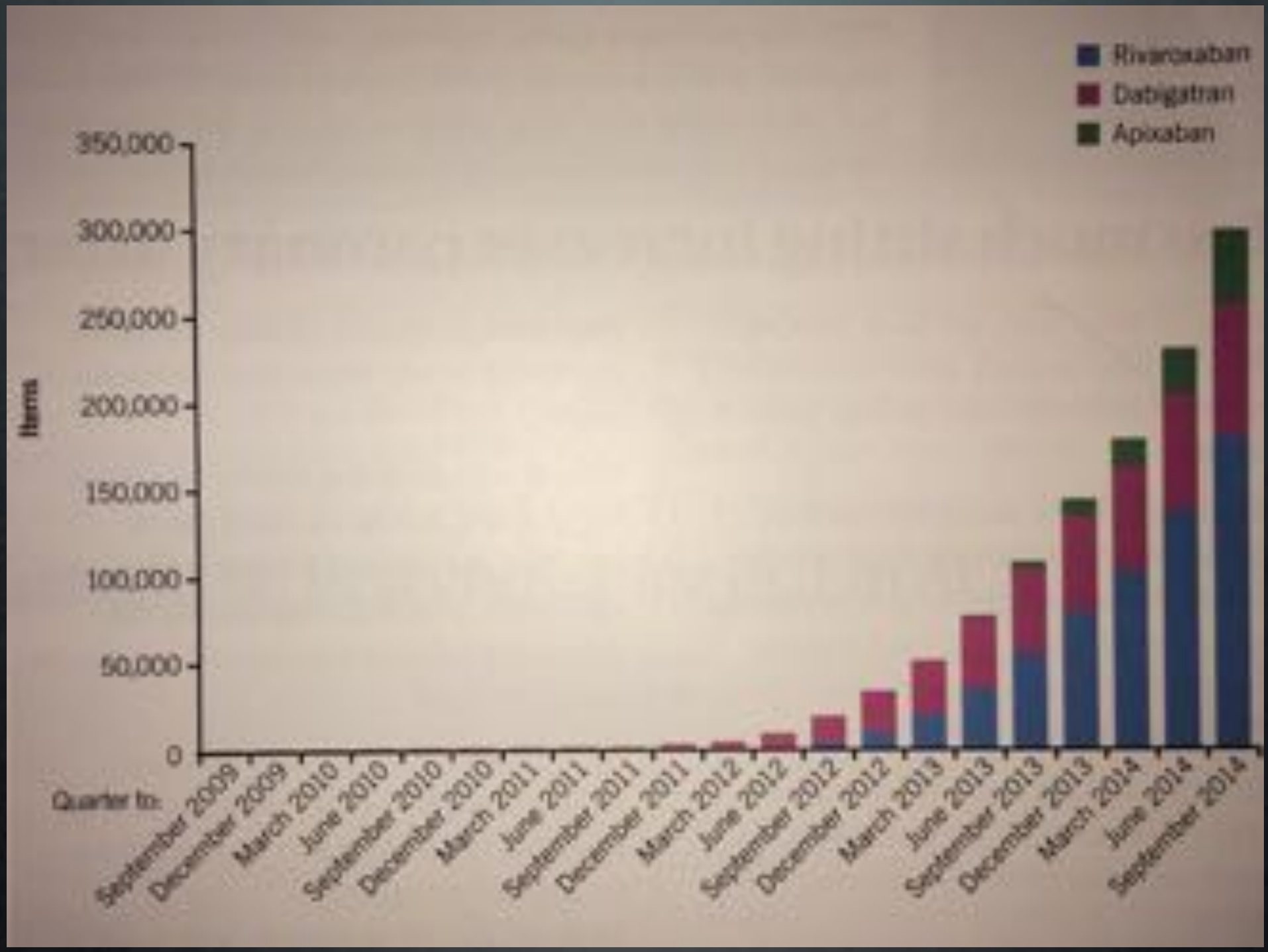
NICE clinical guideline 180

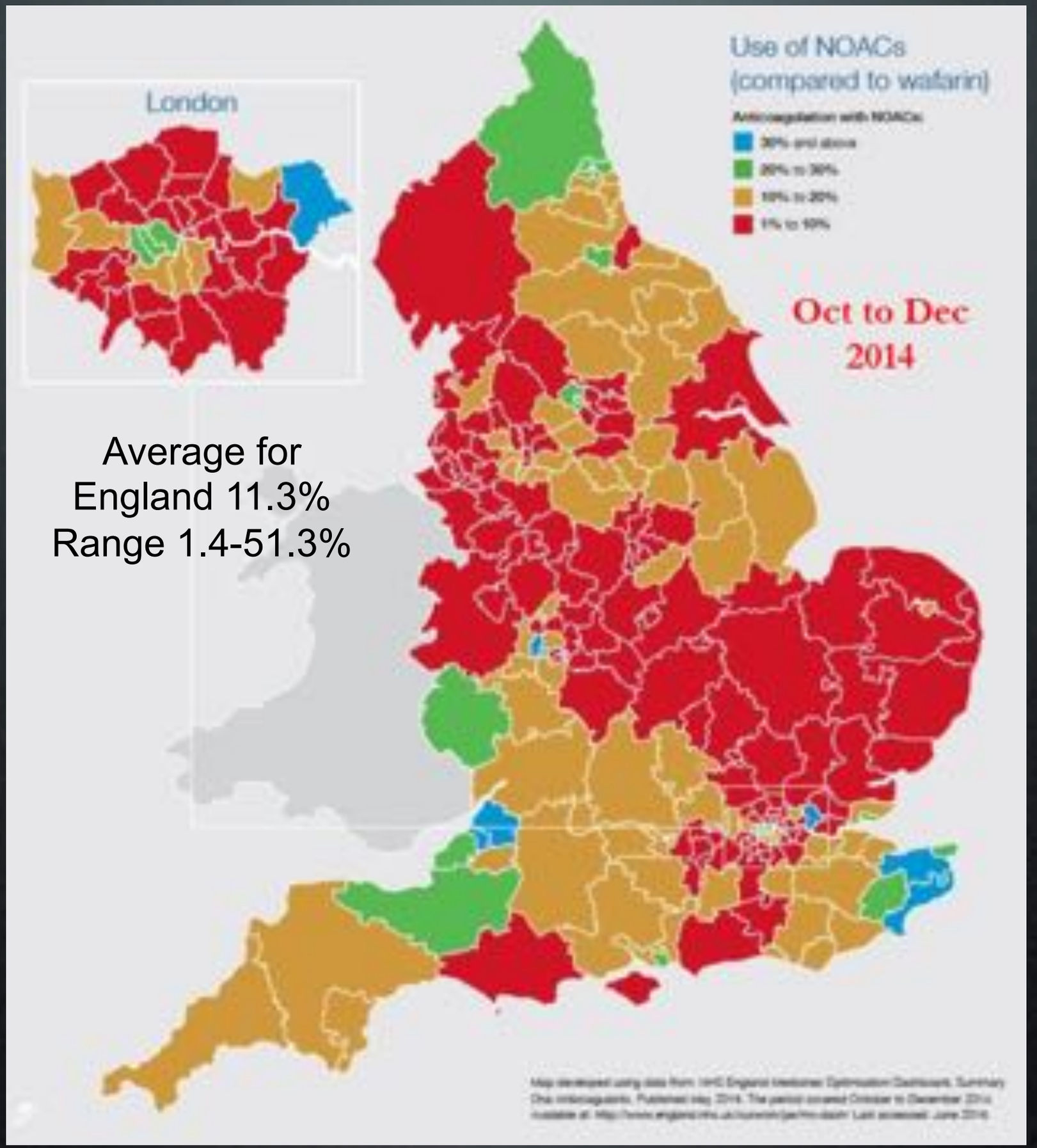
guidance.nice.org.uk/cg180

NICE AF Guideline (2014): Key Messages

- Use CHA2DS2-VASc score to quantify 5-year stroke risk
  - Offer Oral Anticoagulation if score > 1
  - Consider OAC if score=1
- Do not use Aspirin mono-therapy
- Offer Direct Oral Anticoagulants as an option to all
- Assess quality of INR control at each visit
  - Consider switching to DOACs if control poor

NOAC prescriptions for England




London
Use of NOACs
(compared to wafarin)
Oct to Dec
2014
Average for
England 11.3%
Range 1.4-51.3%

Limitations of NOACs

	N	Major Bleeding N (%/yr)	Intracranial bleeding N (%/yr)	Significant GI bleed N (%/year)	Treatment abandoned by 1 year
Dabigatran 150 mg BD	6076	409 (3.4)	38 (0.32)	188 (1.6)	22%
Dabigatran 110 mg BD	6015	347 (2.9)	27 (0.23)	137 (1.2)	20%
Rivaroxaban 20 mg OD	7111	395 (3.6)	55 (0.5)	224 (3.1)	24%
Apixaban 5 mg BD	9088	327 (2.1)	52 (0.33)	105 (0.8)	16%
Edoxaban 60 mg OD	7035	418 (2.8)	61 (0.39)	232 (1.5)	34.4%
Edoxaban 30 mg OD	7034	254 (1.6)	41 (0.26)	129 (0.8)	33%

Real Life Data: Dabigatran

	No. of Events		Incidence Rate per 1000 Person-Years	
	Dabigatran	Warfarin	Dabigatran	Warfarin
Ischemic stroke	205	270	11.3	13.9
Major hemorrhage	777	851	42.7	43.9
Gastrointestinal	623	513	34.2	26.5
Intracranial	60	186	3.3	9.6
Intracerebral	44	142	2.4	7.3
Hospitalized bleeds	1079	1139	59.3	58.8

***Graham et al. Circulation*. 2015;131:157-164**

Real Life Data: Rivaroxaban

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	**Incidence rate, events per 100 patient years (95% CI)***
Major bleeding	128 (1.9)	2.1 (1.8–2.5)
Fatal	12 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	43 (0.6)	0.7 (0.5–0.9)
Intracranial haemorrhage	26 (0.4)	0.4 (0.3–0.6)
Mucosal bleeding#	60 (0.9)	1.0 (0.7–1.3)
Gastrointestinal	52 (0.8)	0.9 (0.6–1.1)
Haemoglobin decrease ≥2 g/dL	52 (0.8)	0.9 (0.6–1.1)
Transfusion of ≥2 units	53 (0.8)	0.9 (0.6–1.1)
Non-major bleeding events	878 (12.9)	15.4 (14.4–16.5)

1. Camm AJ *et al*, *Eur Heart J* 2015*;* doi: 10.1093/eurheartj/ehv466

Stroke/ SE events on NOACs

	N	Ischemic Stroke N (%/yr)	Stroke or Systemic Embolism N (%/yr)
Dabigatran 150 mg BD	6076	112 (0.93)	135 (1.12)
Dabigatran 110 mg BD	6015	159 (1.34)	183 (1.54)
Rivaroxaban 20 mg OD	7111	149 (1.34)	269 (2.1)
Apixaban 5 mg BD	9088	162 (0.97)	212 (1.27)
Edoxaban 60 mg OD	7035	236 (1.25)	296 (1.6)
Edoxaban 30 mg OD	7034	333 (1.7)	383 (2.0)

Rationale for LAA occlusion

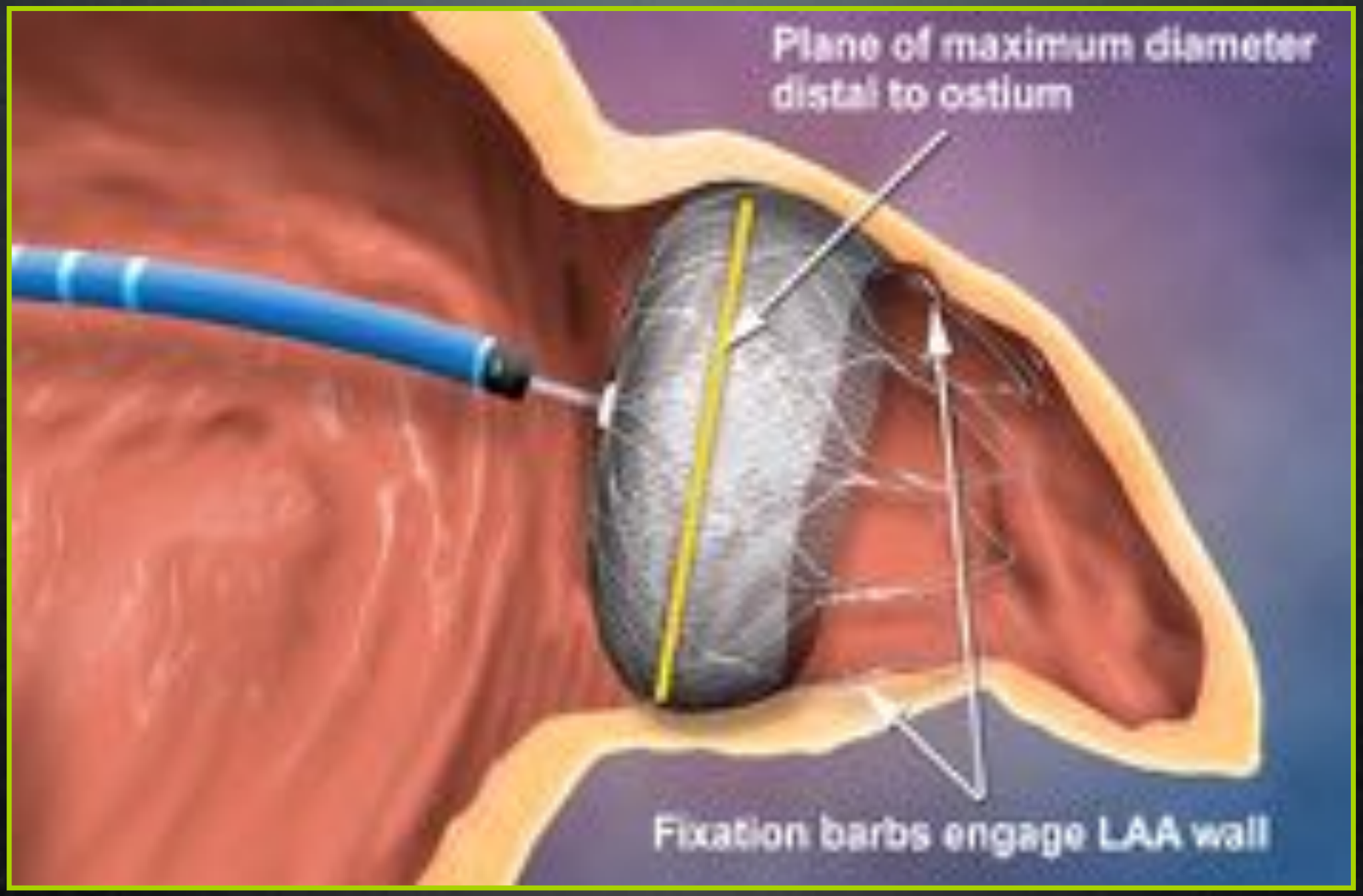
- Insufficient contraction of LAA leads to stagnant blood flow
- Most likely culprit: embolization of LAA clot
- 90% of thrombi found in LAA*
- TEE-based risk factors**
  - Enlarged LAA
  - Reduced inflow and outflow velocities
  - Spontaneous Echo contrast

*Blackshear: Ann Thoracic Surg 61, 1996
**Johnson: Eur J Cardiothoracic Surg 17, 2000

Current LAAO devices

- WATCHMAN device
  - 2 RCTs: PROTECT AF and PREVAIL
  - 2 prospective registries: CAP and CAP2
- Amplatzer Cardiac Plug/ Amulet
  - CE mark for Europe
  - No RCT done or planned
- LARIAT
  - CE mark for Europe
  - Off-label use in USA based on FDA 510(k) approval

WATCHMAN


Plane of maximum diameter
distal to ostium
Fixation barbs engage LAA wall

Watchman: Patient level metaanalysis

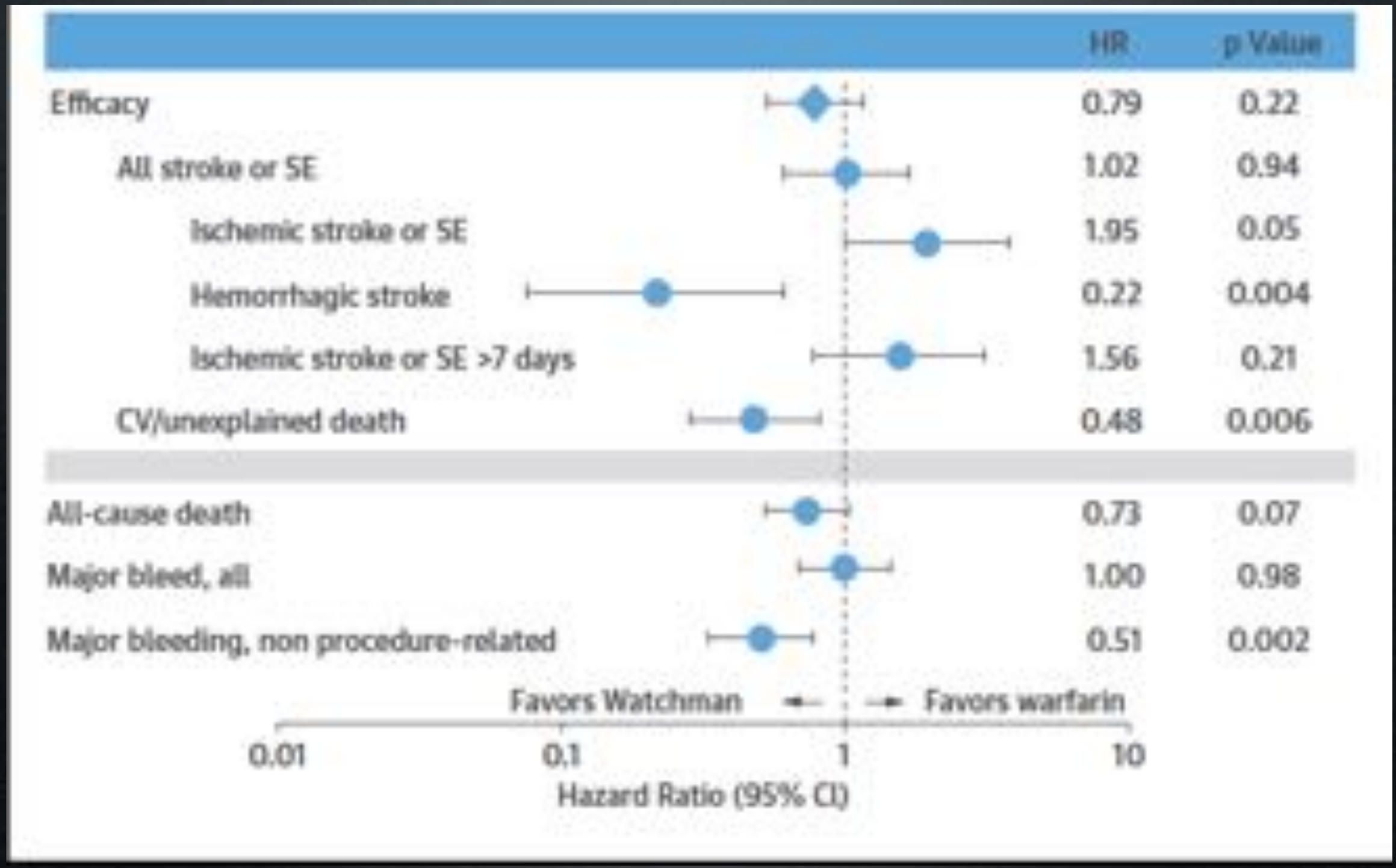
	PROTECT AF	PREVAIL	CAP	CAP2	Total
Enrollment	2005–2008	2010–2012	2008–2010	2012–2014	
Enrolled	800	461	566	579	2,406
Randomized	707	407	—	—	1,114
Watchman: warfarin (2:1)	463:244	269:138	566	579	1,877:382
Mean FU, yrs	4.0	2.2	3.7	0.58	N/A
Patient-years	2,717	860	2,022	332	5,931

(J Am Coll Cardiol 2015;65:2614–23)

Easier and Safer to Implant with time

	PROTECT AF	CAP	PREVAIL	p Value
Implant success	90.0	94.3	95.1	0.04
All 7-day procedural complications	8.7	4.2	4.5	0.004
Pericardial effusion requiring surgery	1.6	0.2	0.4	0.03
Pericardial effusion with pericardiocentesis	2.4	1.2	1.5	0.318
Procedure-related strokes	1.1	0.0	0.7	0.02
Device embolisation	0.4	0.2	0.7	0.368

Comparison to Warfarin



(J Am Coll Cardiol 2015;65:2614–23)

What about patients with Contraindications to OAC? ASAP study

- 150 patients, average age 72
- Mean CHADS 2.8, mean CHADSVASc 4.4
- Reasons for warfarin ineligibility
  - History of hemorrhagic/bleeding tendencies 140 (93.0%)
  - Blood dyscrasia 11 (7.3%)
  - Unsupervised senility/high fall risk 6 (4.0%)
  - Other 8 (5.3%)

V Reddy et al, JACC 2013; 61:2551-6

ASAP study: late complications

Device thrombus on follow up in 6 (4%)

1 Ischemic stroke: 341 days post implant

Others : mean 164±135 d post implant

4 received 4-8 weeks of LMWH

PROTECT AF: device thrombus in 20/473 (4.2%)

V Reddy et al, JACC 2013; 61:2551-6

UK experience with LAAO

- 371 pts from 8 centres between Jul 2009 and Nov 2014
- Mean age 72.9±8.3 years, 61% males
- Median (IQ range) CHADS2, CHA2DS2-VASc and HAS-BLED scores were 3(2-4), 4 (3-5) and 3 (3-4).
- Indication for LAAO
  - previous severe bleeding in 65.4%,
  - HAS-BLED ≥3 in 17.6%,
  - labile INR in 3.2%
  - drug intolerance in 5.1%
  - ischemic stroke despite warfarin in 3.5%
  - lifestyle choice in 5.4%

T Betts et al, Heart Rhythm Sessions 2015, P006-108

UK experience with LAAO

- Periprocedure and early post-operative warfarin 42%
- Watchman device 58.3% and Amplatzer device in 32.1%
- The overall procedure success 92.4%
- Total complication rate 6.7%, Major events 3.8%
- No association between procedural outcomes and device manufacturer or anti-thrombotic regime

T Betts et al, Heart Rhythm Sessions 2015, P006-108

UK experience with LAAO

	2009-2010	2011-12	2013-14	P Value
Implant Success	85.4%	89.3%	96.1%	0.039
Major Complications	7.8%	6.9%	0%	0.004

T Betts et al, Heart Rhythm Sessions 2015, P006-108

Why not LAAO for all AF patients?

	PROTECT AF LAAO	PROTECT AF Warfarin	RE-LY Dabigatran150	ROCKET AF Rivaroxaban	ARISTOTLE Apixaban
Age, years	71.7	72.7	71.5	73	70
CHADS2	2.2	2.3	2.1	3.5	2.1
Major bleeding(%)	3.5	4.1	3.1	3.6	2.1
Stroke/ SE(%)	2.3	2.7	1.1	1.7	1.3

Why not LAAO for all AF patients?

	AVERROES		**BAFTA**	
	APIXABAN	ASPIRIN	WARFARIN	ASPIRIN
Major Bleeding event % per year	1.4	1.2	1.9	2.0
Intracranial	0.4	0.4	0.7	0.5
GI bleeding	0.4	0.4	1.4	1.6
Non-GI major	0.6	0.4		

What do the Scientific Guidelines say?

- ESC 2012 Focussed Update on Management of AF
  - In Patients with high stroke risk who have contraindications to long-term anticoagulation (Class IIb, Level of evidence B)
- ACC/HRS guideline for AF management 2014
  - Silent (pre-FDA approval of Watchman)
- NICE AF guidance 2014
  - Consider LAAO if oral anticoagulation is contraindicated or not tolerated
  - Do not offer as an alternative to OAC

Summary

- Stroke main cause of morbidity in AF
- NOACs are the single biggest advance in AF management
- LAAO should be considered for patients at high risk of bleeding